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COMPOSITION BASED ON PERFLUOROORGANIC COMPOUND EMULSION FOR BIOMEDICAL PURPOSES
[SOSTAV NA OSNOVE EMULSII PERFTORORGANICHESKIKH SOYEDINENIY DLYA MEDIKO-BIOLOGICHESKIKH TSELEY]

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The invention relates to compounds used to obtain emulsions based on perfluoroorganic compounds capable of transferring oxygen and other gases, and can be used in the medical industry as an artificial blood or contrast media, as well as media for the preservation of organs.

Compounds based on perfluorocarbon emulsions as a rule utilize two types of perfluoroorganic compounds simultaneously. One of them is selected from the group (C_8-C_{10}), which contains, for example, perfluorodecalin (PFD) or perfluorooctyl bromide (PFOB), the second from the group (C_{11}-C_{12}), which contains, for example, perfluorotripropyl amine (PFTPA), perfluoromethyl cyclohexyl piperidine (PFMCP), or perfluorotributyl amine (PFTBA). These perfluorocarbons dissolve about 40% by volume of oxygen (with pO_2 = 760 mmHg) and 150-190% by volume of carbon dioxide (pO_2 = 760 mmHg), with the result that they began to be used as the main component of a gas carrier in the development of artificial blood. However, perfluoroorganic compounds (PFOC) are not soluble in water or other liquids, so they can be used solely in the form of emulsions with a specific size of perfluorocarbon particles, coated with a layer of emulsifier (proxanol), and the smaller the size of the emulsion particle, the better, since emulsions are injected intravenously, and if they are large, they could cause an embolism (blockage) of the

vessels. Compounds of the first type are quickly eliminated from the organism, but adequate stability of their emulsions is not assured, while compounds of the second type impart high stability to the emulsions, making it possible to store them without freezing, but are not eliminated from the organism for several years.

An emulsion composition is known which contains, for example, perfluorodecalin (PFD) and perfluorotripropyl amine (PFTPA); emulsifying agents, for example a copolymer of polyoxyethylene-propylene (Pluronik F-68, the Russian analog of proxanol), phospholipids of egg yolk or soy lipids, and water (USSR patent N-797546, published in the bulletin "Discoveries, Inventions…," 1981, N2). According to this composition, the concentration of perfluorocarbons is 24% in a physiologically acceptable aqueous medium.

Among the deficiencies of this invention one must include the fact that the emulsion composition has particles which are rather coarsely dispersed in terms of size, and cannot be stored in unfrozen form.

In the composition of the other emulsion of the same company, prepared for medical purposes on the basis of PFD and PFTPA, which is called Fluosol-DA 20%, the average size was much less than that of the previous emulsion and was 0.118 μm, while the percentage of particles from 0.2 to 0.5 μm in size was 7.8%.

Proxanol and phospholipids of egg yolk were used in the composition as an emulsifier.

However, the average particle size in a composition of this emulsion was also large owing to the fact that at high temperatures in the emulsification and sterilization process, the emulsion particles are consolidated. In addition, the perfluorocarbons used in the composition consolidate rather quickly (Mitsuno T. et al, "Intake and retention of perfluorochemical substance of Fluosol-DA in res human," Proceedings of the 5th Int. Sympos. on Oxygen-Carrying Colloidal Blood Substitutes, Mainz, March, 1981, p 220). This emulsion composition is stored only in frozen form, since after 8-12 hours of storage at room temperature, the emulsion particles consolidate and consequently cannot be used for clinical purposes.

There is a known composition of perfluorocarbon emulsions for medical purposes (RF Patent N-2070033, published in 1996, N 34), similar to the claimed composition, which contains perfluorodecalin or perfluorooctyl bromide and perfluoromethyl cyclohexyl piperidine in a ratio of 2/1 and concentration of from 20 to 40% with an average particle size from 0.06 to 0.11 μm.

The maximally acceptable average size of emulsion particles of 0.11 μm is a drawback of this composition. In addition, an

emulsion of this composition contains coarsely dispersed particles with a diameter from 0.2 to 0.4 μm in a quantity of 0.4% (Table 1), which can increase the number of reactogenic (secondary) reactions.

However, the chief deficiency of this composition is the extended presence of the perfluorocarbons themselves in the organs and tissues of the organism, which can last for 18-24 months.

A composition of perfluorocarbon emulsion for medical and biological purposes (RF Patent N 2122404, published in 1998, N 33) is closest to the claimed composition. It contains perfluorodecalin, perfluoromethyl cyclohexyl piperidine, perfluorooctyl bromide, and perfluorotributyl amine, emulsified by 4% proxanol 268 to an average emulsion particle size of 0.03-0.05 μm.

A deficiency of this composition is the extended presence of perfluorocarbons in the organs and tissues of the organism, lasting for 18-24 months. Another important factor related to the deficiencies of this composition is the secondary reactions, which are less than in the prior composition (RF Patent N 2070033, published in 1996, No 34) by 10%, but still are rather high at 20% (Table 1).

The object of the invention is to create a composition based on a perfluorocarbon emulsion for biomedical purposes, with a

reduction in the quantity of secondary reactions and with a short presence of the perfluoroorganic compounds in the organism.

This object is achieved in that, in the claimed composition on the basis of a perfluorocarbon emulsion for biomedical purposes, which includes production of the PFOC emulsion by the mixing of diverse perfluoroorganic compounds with proxanol, the emulsifying agent (or phospholipids) with subsequent homogenization of the obtained mixture, in accordance with the invention, a perfluorocarbon emulsion consisting of a mixture of two PFOC: perfluorodecalin (PFD)/ perfluoromethyl cyclohexyl piperidine (PFMCP) or PFD / perfluorotributyl amine (PFTBA) or perfluorooctyl bromide

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(PFOB)/PFTBA, or PFOB/PFMCP in a ratio of 1/1 to 10/10 respectively; or from a mixture of three PFOC: PFOB/PFD/PFMCP or PFOB/PFD/PFTBA in a ratio from 1/1/1 to 10/10/10 respectively; or from a mixture of four PFOC: PFOB/PFD/PFMCP/PFTBA in a ratio of from 1/1/1/1 to 10/10/10/10 respectively, also contains a physiologically acceptable electrolyte solution in the following concentrations of ingredients in the emulsion: sodium chloride - 6.0-9.0 g/l; potassium chloride - 0.39-0.41 g/l; magnesium chloride (in terms of the dry substance) - 0.19-0.21 g/l; sodium hydrocarbonate - 0.65-0.68 g/l; monosubstituted sodium phosphate (in terms of the dry substance) - 0.2-0.23 g/l; glucose - 2.0-

2.2 g/l; proxanol from 0.4% to 4.8%; perfluorocarbons from 1% to 20%.

The ratio of perfluorocarbons was selected with allowance for experimental investigations. Thus, in order to increase the stability of perfluoro-emulsions during storage, the emulsion must always contain perfluorocarbons which create stable emulsions, but are hard to eliminate from the organism. These are PFMCP or PFTBA. To increase the concentration of PFOC in the emulsion, the readily eliminated PFD or PFOB are added to the poorly eliminated PFMCP and PFTBA, but these accordingly produce unstable emulsions. Based on these studies, various emulsion compositions were found with a different ratio and quantity of perfluorocarbons and accordingly with different positive properties. The proposed composition, on the basis of perfluorocarbon emulsions, makes it possible to create perfluorocarbon emulsions with a low degree of reactogenicity (the secondary reactions are reduced by half in comparison with the analogous method), since in the diluted emulsion, there is a significant decrease in the quantity of coarsely dispersed particles capable of triggering secondary negative reactions, owing to the reduction in the total number of all particles of the emulsion from $1.5 \cdot 10^{18}$ to $0.75 \cdot 10^{18}$ (Table 1). All this helps to promote safer use of perfluorocarbon blood replacements in medicine and to expand the fields of their application

(ultrasound, radiographic, and magnetic resonance examinations). Another important factor in improving the quality of the emulsion in the proposed composition is the increase in the speed of elimination of the perfluorocarbons proper from organs and tissues, in comparison with the analogous method. Thus PFOC are retained in the organs and tissues for around 18-24 months after injection of the emulsion analog. In the proposed composition, PFOC leave the organism twice as fast, in 9-12 months (Table 1), which is very important in medical practice and has an undoubted advantage over other analogous compositions.

Thus the proposed composition based on an emulsion of perfluoroorganic compounds for biomedical purposes is much more preferable, in comparison with an analogous composition and the composition of the Japanese preparation, Fluosol-DA 20%.

Production of a 10% (5% by volume) composition of the emulsion

Example 1. A perfluorocarbon mixture of PFD/PFMCP in a ratio of 2/1, in a quantity of 200 ml, containing 266 g of PFD of specific density 1.938 and 133 g of PFMCP of specific density 1.920 was passed through a homogenizer with a 10-12% solution of proxanol in a quantity of 800 ml. After this, the PFOC and proxanol mixture obtained was diluted with 3,000 ml of concentrated electrolyte solution, maintaining the osmotic

pressure. The average particle size of the emulsion was 0.045 μm.

The final formulation of the perfluorocarbon emulsion had the following composition: PFD/PFMCP (ratio 2/1) – 10% (5% by volume), proxanol - 2-2.4%, sodium chloride - 6.0-9.0 g/l; potassium chloride - 0.39-0.41 g/l; magnesium chloride (in terms of the dry substance) - 0.19-0.21 g/l; sodium hydrocarbonate - 0.65-0.68 g/l; monosubstituted sodium phosphate (in terms of the dry substance) - 0.2-0.23 g/l; glucose - 2.0-2.2 g/l. The emulsion obtained can be used as a blood-replacement substance for intravenous injection and for internal use, as well as a medium during ultrasound and magnetic resonance investigations and for external use.

Example 2. A composition based on the emulsion was prepared as described in example 1. The ratio of PFOB/PFD/PFTBA was 10/2/1, the weights of PFOB/PFD/PFTBA were 307/62/31 g respectively. The average size of the emulsion particles was 0.042 μm.

The final formulation of the perfluorocarbon emulsion had the following composition: PFOB/PFD/PFTBA (ratio 10/2/1) - 10% (5% by volume), proxanol - 2-2.4%, sodium chloride - 6.0-9.0 g/l; potassium chloride - 3.39-0.41 g/l; magnesium chloride (in terms of the dry substance) - 0.19-0.21 g/l; sodium hydrocarbonate - 0.65-0.68 g/l; monosubstituted sodium phosphate (in terms of the

dry substance) - 0.2-0.23 g/d; glucose - 2.0-2.2 g/l. The emulsion obtained can be used as a blood replacement and contrast medium with intravenous injection and internal use.

Example 3. A composition based on the emulsion was prepared as described in example 1. The ratio of PFOB/PFD/PFMCP/PFTBA was 10/1/1, the weights of the PFOB/PFD/PFMCP/PFTBA were respectively 182/182/18/18 g. The average particle size of the emulsion was 0.050 μm.

The final formulation of the perfluorocarbon emulsion had the following composition: PFOB/PFD/PFMCP/PFTBA (ratio 10/10/1/1) - 10% (5% by volume), proxanol - 2-2.4%, sodium chloride - 6.0-9.0 g/l; potassium chloride - 0.39-0.41 g/l; magnesium chloride (in terms of the dry substance) - 0.19-0.21 g/l; sodium hydrocarbonate - 0.65-0.68 g/l; monosubstituted sodium phosphate (in terms of the dry substance) - 0.2-0.23 gl; glucose - 2.0-2.2 g/l. The emulsion obtained can be used as a blood replacement and contrast medium with intravenous injection and for internal use.

Production of a 1% composition (0.5% by volume) of the emulsion.

Example 4. A composition based on the emulsion was prepared as

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described in example 1. The ratio of PFD/PFMCP was 2/1 in a quantity of 200 ml, the weights of PFD/PFMCP were 266/133 g respectively. The specific density of the PFD was 1.938. The specific density of the PFMCP was 1.920. The average size of the emulsion particles was 0.031 μm.

The emulsion obtained is diluted with 39,000 ml of concentrated electrolyte solution, which maintains the osmotic pressure.

The final formulation of the perfluorocarbon emulsion had the following composition: PFD/PFMCP (ratio of 2/1) - 1% (0.5% by volume), proxanol - 0.4-0.6%, sodium chloride - 6.0-9.0 g/l; potassium chloride - 0.39-0.41 g/l; magnesium chloride (in terms of the dry substance) - 0.19-0.21 g/l; potassium hydrocarbonate - 0.65-0.68 g/l; monosubstituted potassium phosphate (in terms of the dry substance) - 0.2-0.23 g/l; glucose - 2.0-2.2 g/l. The emulsion obtained can be used as a blood replacement and contrast medium with intravenous injection and for internal and external use.

Production of a composition of 20% (10% by volume) emulsion.

Example 5. A composition based on the emulsion was prepared as described in example 1. The ratio of PFD/PFMCP was 2/1 in a quantity of 200 ml, the weights of PFD/PFMCP were 266/133 g respectively. The specific density of PFD was 1.938. The

specific density of PFMCP was 1.920. The average size of the emulsion particles was 0.05 μm.

The emulsion obtained is diluted with 1,000 ml of concentrated electrolyte solution, maintaining the osmotic pressure.

The final formulation of the perfluorocarbon emulsion had the following composition: PFD/PFMCP (ratio 2/1) - 20% (10% by volume), proxanol - 4-4.8%, sodium chloride - 6.0-9.0 g/l; potassium chloride - 0.39-0.41 g/l; magnesium chloride (in terms of the dry substance) - 0.19-0.21 g/l; sodium hydrocarbonate - 0.65-0.68 g/l; monosubstituted sodium phosphate (in terms of the dry substance) - 0.2-0.23 g/l; glucose - 2.0-2.2 g/l. The emulsion obtained can be used as a blood replacement and contrast medium with intravenous injection for internal and external use.

Claims:

1. A composition based on emulsions of perfluoroorganic compounds (PFOC) for biomedical purposes, including various perfluoroorganic compounds and proxanol or phospholipids, characterized in that the perfluorocarbon emulsion consisting of a mixture of two perfluoroorganic compounds (PFOC): perfluorodecalin (PFD)/perfluoromethyl cyclohexyl piperidine (PFMCP) or PFD/perfluorotributyl amine (PFTBA) or perfluorooctyl bromide (PFOB)/PFTBA or PFOB/PFMCP in a ratio of from 1/1 to

10/10 respectively, or of a mixture of three PFOC: PFOB/PFD/PFMCP or PFOB/PFD/PFTBA in a ratio of from 1/1/1 to 10/10/10 respectively, or of a mixture of four PFOC: PFOB/PFD/PFMCP/PFTBA in a ratio of from 1/1/1/1 to 10/10/10/10 respectively, also contains a physiologically acceptable electrolyte solution with the following concentrations of ingredients in the emulsion: sodium chloride 6.9-9.0 g/l; potassium chloride 0.39-0.41 g/l; magnesium chloride (in terms of the dry substance) 0.19-0.21 g/l; sodium hydrocarbonate 0.65-0.68 g/l; monosubstituted sodium phosphate (in terms of the dry substance) 0.2-0.23 g/l; glucose 2.0-2.2 g/l; proxanol from 0.4 to 4.8%, perfluorocarbons from 1 to 20%.

2. An emulsion composition in accordance with claim 1, characterized in that the emulsion is intended for intravenous and intra-arterial injection and before use is diluted from 1.5 to 10 times with any solution or composition compatible with the emulsion.

3. An emulsion composition in accordance with claims 1 and 2, characterized in that the emulsion is intended for peroral, intracavitary, and external use.

4. An emulsion composition in accordance with claims 1-3, characterized in that before use the emulsion is saturated with any gas or mixture of gases.

5. An emulsion composition in accordance with claims 1-4, characterized in that the emulsion is intended for use as contrast media in ultrasound, radiographic, or magnetic resonance examinations.

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Table 1. Distribution of particles by diameter and average size of particles of emulsions of perfluorocarbons and some of their biological characteristics

Particle diameter (μm)	Analogous compound Fluosol-DA 20% 20% emulsion	Analogous compound 1: PFD/PFMCP (2/1) 20% emulsion	Analogous compound 2: PFD/PFMCP (2/1) 20% emulsion	Claimed composition PFD/PFMCP (2/1) 10% emulsion
	Particle distribution (%)			
less than 0.1	39.2	85.2	87.1	87.1
0.1-0.2	53.0	14.4	12.6	12.7
0.2-0.3	5.9	0.4	0.3	0.2*
0.3-0.4	1.5	-	-	-
0.4-0.5	0.4	-	-	-
Average size (μm)	0.118	0.06-0.11	0.03-0.05	0.03-0.05
Absolute quantity of particles in 1 liter (ea)	-	$1.5 \cdot 10^{18}$	$1.5 \cdot 10^{18}$	$0.75 \cdot 10^{18}$**
Elimination of PFOC from the organism (months)	-	18-24	18-24	9-12***
Secondary reactions (%)	-	30	20	10****

where: *number of aggregated dispersed particles is reduced;
**absolute number of particles is reduced;
***time of PFOC in organism is reduced;
****quantity of secondary reactions is reduced.